Immune Checkpoint Inhibition for Pancreatic Cancer

Seyed Aria Nejadghaderi[1,2], Sepideh Razi[1,3], Mahsa Keshavarz-Fathi[1,4], Nima Rezaei[5,6,7]

[1] *Cancer Immunology Project (CIP), Universal Scientific Education and Research Network (USERN), Tehran, Iran*

[2] *Student Research Committee, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran*

[3] *Student Research Committee, School of Medicine, Iran University of Medical Sciences, Tehran, Iran*

[4] *School of Medicine, Tehran University of Medical Sciences, Tehran, Iran*

[5] *Research Center for Immunodeficiencies, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran*

[6] *Department of Immunology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran*

[7] *Cancer Immunology Project (CIP), Universal Scientific Education and Research Network (USERN), Stockholm, Sweden*

Received: 26 Feb. 2022; Accepted: 18 Jan. 2023

Abstract- Pancreatic cancer is one of the ten most lethal cancers with a mortality rate of 5.7 per 100,000 individuals worldwide. According to the disease stage, its 5-year survival rate is between 3% and 34%. Treatment options for pancreatic cancer are surgery, chemotherapy, radiotherapy, and immunotherapy. Immune checkpoint inhibitor therapy is a kind of immunotherapy. Immune checkpoints on T cells like cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) and programmed cell death protein-1 (PD-1) suppress the immune system by attaching to their ligands on normal and/or tumor cells. This mechanism protects the body against immune system hyperactivity, especially in autoimmune diseases, but tumor cells can escape from immune responses by expressing these ligands to maintain in the body and to be safe against the immune system. Immune checkpoint inhibitors are immunotherapeutic drugs that bind to proteins in cancer cells to prevent them from suppressing the immune system. Immune checkpoint inhibitors may lead to some adverse effects like vitiligo, thyroiditis, adrenal insufficiency, and other ophthalmologic, hematologic, and respiratory problems. However, it has been shown that the combination of these therapies with each other or other therapeutic approaches could increase the safety and efficacy of this developing method. Here, we will review some trials that have been done or are ongoing about the advances and the effects of immune checkpoint inhibitors on patients with pancreatic cancer.

Acta Med Iran 2023;61(3):128-144.

Keywords: Immune checkpoint inhibitors; Pancreatic cancer; Immunotherapy; Cluster of differentiation 152 (CD152); Cluster of differentiation 279 (CD279); Cluster of differentiation 274 (CD274)

Introduction

The World Health Organization (WHO) estimates that 9.6 million people died from cancer in 2018 worldwide (1), and it has been reported that pancreatic cancer was among the five most lethal cancers in the United States in 2019 (2). Pancreatic ductal adenocarcinoma (PDAC) and pancreatic neuroendocrine tumors (pNETs) are the two common types of pancreatic cancer that are responsible for 90% and 5% of pancreatic cancer occurrence, respectively (1). There are several risk factors for this cancer, including consumption of red and processed meat in men, obesity, especially in men, tobacco and alcohol usage, and green tea (3-5). It is worth mentioning that there are also some protective factors against pancreatic cancer, such as having fruit and vegetables and a waist circumference equal to or less than 75 cm (4,6).

The pancreas has two parts, including exocrine and endocrine parts. The exocrine part of the pancreas consists of ducts that release enzymes into the second part of the small intestine. PDAC results from the uncontrolled growth of mucin-producing glandular structures of the exocrine part of the pancreas (7). Additionally, there are rare types of pancreatic cancer that

Corresponding Author: N. Rezaei
Research Center for Immunodeficiencies, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran
Tel: +98 2166929234, E-mail addresses: rezaei_nima@tums.ac.ir, rezaei_nima@yahoo.com

originate from the exocrine part of the pancreas, including cystic neoplasm, intraductal papillary mucinous tumor, acinar cell carcinoma, pleomorphic carcinoma, and epithelial neoplasm (8). Langerhans or islet cells constitute the endocrine part of the pancreas and secrete insulin and glucagon hormones into the blood. If endocrine cells become cancerous, pNETs such as insulinoma and gastrinoma will occur (8,9).

Malignant pancreatic tumors are typically diagnosed in the advanced or metastatic stage because the pancreas is in the posterior part of the abdomen, and its symptoms can be vague (10). There are several options for the treatment of patients with pancreatic cancer such as surgery, chemotherapy, radiotherapy, and immunotherapy. In the surgical method, the size, type, and location of pancreatic tumors determine which pancreatic surgery, such as enucleation, distal pancreatectomy, and pancreatoduodenectomy is appropriate. However, there is a high chance of tumor recurrence with this method (11). Chemotherapy is another treatment option. 5-fluorouracil (5-FU) was the first drug that had been used for the treatment of advanced pancreatic cancer (12). Gemcitabine is another chemotherapeutic drug that was widely used for patients with cancer, but it had some adverse effects such as nausea, vomiting, diarrhea, anemia, and neutropenia (13,14). FOLFIRINOX is a combination of four drugs, including 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin, and is more efficient than gemcitabine in the treatment of metastatic or advanced pancreatic adenocarcinoma (15-18). In other words, a modified FOLFIRINOX could increase the median disease-free survival for about nine months in comparison with gemcitabine alone (21.6 vs. 12.8 months) (14). Also, the progression-free survival (PFS) of FOLFIRINOX in stage III and IV metastatic or locally advanced pancreatic cancer is about seven months (14). Thus, combination therapies are now rising, which are safer and more efficient than monotherapies in the treatment of patients with cancer (19,20). Another option for the treatment of patients with pancreatic cancer is radiation therapy such as intensity-modulated radiation therapy which uses a lower dose of radiation beams than image-guided radiation therapy to increase treatment accuracy and the quality of life and to reduce side effects, intense and delayed-occurring toxicities (21-23). Stereotactic body radiation therapy that uses high doses of radiation in short periods leads to the median overall survival (OS) and PFS of 16.7 and 10.2 months in locally advanced pancreatic cancer, respectively (24). Recently, a non-invasive therapeutic method called proton beam therapy has been also used for the treatment of patients with pancreatic cancer. It has been reported that the proton beam therapy radiation dose is more concentrated on target organs so that the entrance dose decreases and there is no exit dose (25). However, different types of radiotherapy have some adverse effects, such as gastrointestinal bleeding, perforation, obstruction, thrombocytopenia, and anemia. Therefore, other therapies with lower toxicities are needed (26,27).

Immunotherapy stimulates or improves the immune system to attack tumor cells. Tumor cells can escape from the immune system by using some mechanisms, including secretion of immunosuppressive agents, inhibiting presentation of major histocompatibility complex (MHC) class I, and expressing immune checkpoints like programmed cell death protein-ligand (PDL)-1. Immune checkpoint inhibitors are a kind of immunotherapeutic agent which can block immune checkpoints (28). The first kind of immune checkpoint inhibitors that got approved by the Food and Drug Administration (FDA) was an anti-cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) antibody named ipilimumab for the treatment of patients with melanoma. After that, other immune checkpoint inhibitors like anti-programmed cell death protein (PD)-1 and anti-PDL-1 were approved for a variety of other cancers like gastric or gastroesophageal junction adenocarcinoma, locally advanced or metastatic urothelial carcinoma, and metastatic Merkel cell carcinoma (29-32). Immune checkpoint inhibitors may have some side effects like gastrointestinal adverse events (AEs) that are very common, skin-related AEs such as dermatitis, and other AEs which could affect ophthalmologic, hematologic, respiratory, and endocrinological systems (33-35).

Here, we will review some trials that administrated immune checkpoint inhibitors for the treatment of patients with pancreatic cancer.

Materials and Methods

A systematic search has been conducted using terms including, ("Pancreatic neoplasms" OR “Pancreatic Cancer”) AND ("Therapeutics" OR “Therapy” OR “Treatment”) AND ("Ipilimumab" OR "Nivolumab" OR "Pembrolizumab" OR "Atezolizumab" OR "Avelumab") in PubMed, Scopus, and Web of Science databases. No publication date or study type limit was applied to the search. We also searched the reference lists of the retrieved studies for the identification of potentially relevant studies. We used the following

inclusion criteria: 1) studies conducted on adult patients with pancreatic cancer, 2) studies involved at least one type of immune checkpoint inhibitors like anti-CTLA-4 (e.g., ipilimumab), anti-PD-1 (e.g., pembrolizumab and nivolumab), or anti-PDL-1 (e.g., atezolizumab and durvalumab) monoclonal antibodies, and 3) studies evaluated the safety or efficacy of immune checkpoint inhibitors. Moreover, we searched the www.clinicaltrials.gov website for ongoing clinical trials using immune checkpoint inhibitors for pancreatic cancer. The details of the search strategy for each database have been shown in table S1.

Immune system and pancreatic cancer

The tumor microenvironment (TME) which is a network of immunologic and non-immunologic agents like T cells, macrophages, dendritic cells (DCs), B cells, neuroendocrine cells, endothelial cells, and fibroblasts, has an important role in tumor progression, invasion, and metastasis (36). Some of these cells could induce cancer progression which leads to poor prognosis in patients with pancreatic cancer. For example, the level of regulatory T cells (T-reg) that can promote cancer progression is high in pancreatic cancer patients (37). In addition, it has been shown that myeloid-derived suppressor cells (MDSC) which inhibit both innate and acquired immune systems, and tumor-associated macrophages (TAM) which induce the conversion of pro-inflammatory macrophages to anti-inflammatory macrophages, are increased in pancreatic cancer patients (38,39). While, natural killer (NK) cells that have anti-tumor activities are decreased in patients with pancreatic cancer (40). Some of the immunological cells such as cytotoxic T cells, T-helper type 1 (Th1), DCs, activated pro-inflammatory macrophages, and NK cells have anti-tumor activities and could attack the TME (29). Therefore, the immune system could be stimulated to attack the tumor cells. There are three types of immunotherapeutic methods: the first method is nonspecific stimulation of the immune system like immune checkpoint inhibitors which also has been considered as a passive immunotherapy-based method. The second one is to activate the immune system to attack the cancerous cells such as cancer vaccines and the last method is to administer activated immune cells to the body. These two last methods have also been categorized as active immunotherapeutic approaches (41). Immune checkpoints are agents that regulate immune responses to prevent hyperactivation of the immune system which leads to some complications such as autoimmune diseases. There are immune checkpoints like CTLA-4 and PD-1 on T cells that bind to their ligands including CD80, CD86, and PDL-1 on antigen-presenting cells (APCs) which lead to the suppression of the immune system so that the tumor cells can survive, grow and divide. In these cases, some agents named immune checkpoint inhibitors can be used to prevent this from happening (42-44). Immune checkpoint inhibitors such as ipilimumab and nivolumab bind to CTLA-4 and PD-1 respectively and prevent them from binding to CD80, CD86, and PDL-1 (45). Immune checkpoint inhibitors are proteins with high diversity including anti-CTLA-4 antibodies like ipilimumab, anti-PD-1 antibodies such as nivolumab, pembrolizumab, avelumab, and durvalumab, and anti-PDL-1 antibodies like atezolizumab and avelumab (46). Several kinds of biomarkers can be used to predict the response to treatment and cancer prognosis (47). For instance, it has been shown that the high expression of PDL-1 on tumor cells is associated with poor prognosis in pancreatic cancer (48). In contrast, there is a positive correlation between high numbers of tumor-infiltrating lymphocytes and nivolumab efficacy in cancers like colorectal cancer, melanoma, and renal cell carcinoma (RCC) because the response rate to anti-PD-1 therapy can be predicted by infiltrating immune cells (49). Additionally in blood tests, the high level of lactate dehydrogenase indicated better response to ipilimumab therapy in patients with metastatic melanoma (50). The PDL-1 immunohistochemistry can predict the response to anti-PD-1 and anti-PDL-1 therapies and different immunohistochemistry platforms are used to assess the expression of PD-1 and PDL-1 on tumor cells or tumor-infiltrating cells (51). The response to atezolizumab in metastatic urothelial carcinoma was higher in patients with a high level of mutation load (32). Also, the level of DNA mismatch repair and microsatellite instability can predict responses to nivolumab and pembrolizumab in patients with metastatic cancers (52,53).

Cytotoxic T-lymphocyte Antigen-4 (CTLA-4)
Ipilimumab

Ipilimumab is an anti-CTLA-4 monoclonal antibody. It has beneficial effects on melanoma, and it was the first immunotherapeutic drug that the FDA approved to treat patients with melanoma in 2011 (54), and currently, ipilimumab is used for the treatment of melanoma (55,56).

A Phase Ib/II interventional clinical trial (NCT03404960) is ongoing on 84 patients with advanced pancreatic adenocarcinoma. Arm A of this study consists of patients who are getting niraparib and

nivolumab, and patients in Arm B are getting niraparib and ipilimumab. The goal of this trial is to measure PFS six months after the beginning of the therapy (57). In another study, two immune checkpoint inhibitors named ipilimumab and nivolumab were used for a phase Ⅱ randomized clinical trial on 160 metastatic pancreatic or biliary tract cancer patients, which is proof of the progressive trend of immune checkpoint usage. Nivolumab and radiation therapy were administered for the first arm, whereas ipilimumab, nivolumab, and radiation therapy were used for the other one. The goal of this study is to determine the clinical advantages, OS, and quality of life. Since they gave ipilimumab to patients in one of the arms, it may be possible to determine if the ipilimumab is effective for the treatment of patients with pancreatic cancer (58). Additionally, in another single-arm phase Ⅱ trial, the combination of ipilimumab and nivolumab was injected intravenously into patients with rare tumors (59). There are many other ongoing clinical trials to evaluate the safety and efficacy of ipilimumab (Table 1).

Table 1. Ongoing trials on Ipilimumab

Trial number	Trial type	Phase	Status	Estimated N	Trial design	Treatment arms	Patient population	Drug	Results
NCT03104439	Interventional	Ⅱ	Recruiting	80	N/A	A: Nivolumab, Ipilimumab B: Nivolumab, Ipilimumab, radiation therapy	Microsatellite stable CC PC MSI high CC	Nivolumab, Ipilimumab	N/A
NCT03190265	Interventional	Ⅱ	Recruiting	63	Randomized	A: CY, Nivolumab, Ipilimumab, GVAX, CRS-207 B: Nivolumab, Ipilimumab, CRS-207	PC	CY, Nivolumab, Ipilimumab, GVAX, CRS-207	N/A
NCT02866383	Interventional	Ⅱ	Recruiting	160	Randomized	A: Nivolumab, Radiation therapy B: Nivolumab, Ipilimumab, Radiation therapy	Metastatic PC Metastatic biliary tract cancer	Nivolumab, Ipilimumab	N/A
NCT01473940	Interventional	I	Active, not recruiting	21	N/A	A: Ipilimumab, Gemcitabine	PDAC Recurrent PC Stage ⅢⅣ PC	Ipilimumab, Gemcitabine	N/A
NCT01896869	Interventional	Ⅱ	Suspended	83 (A)	Randomized	A: Ipilimumab, GVAX B: FOLFIRINOX	Metastatic PAC	Ipilimumab, GVAX, FOLFIRINOX	N/A
NCT03098160	Interventional	I	Recruiting	69	N/A	A: Evofosfamide, Ipilimumab	PC Melanoma Head and neck cancer Prostate cancer	Evofosfamide, Ipilimumab	N/A
NCT03404960	Interventional	I/Ⅱ	Recruiting	84	Randomized	A: Niraparib, Nivolumab B: Niraparib, Ipilimumab	PAC	Niraparib, Nivolumab, Ipilimumab	N/A
NCT03373188	Interventional	I	Recruiting	32	Randomized	A: Surgery B: VX15/2503, Surgery C: VX15/2503, Ipilimumab, Surgery D: VX15/2503, Nivolumab, Surgery	Colon carcinoma CC PAC Resectable PC Stage ⅠⅡⅢⅣ PC Stage ⅣCC	VX15/2503, Ipilimumab, Nivolumab	N/A
NCT03695835	Observational	Ⅱ	Active, not recruiting	18 (A)	N/A	A: Ipilimumab, Ablation	Adenocarcinoma	Ipilimumab	N/A

N/A: Not available, IV: Intravenous, N: Number of participants, A: Acute, PC: Pancreatic cancer, CC: Colorectal cancer, CY: Cyclophosphamide, MSI: Microsatellite instability, PDAC: Pancreatic ductal adenocarcinoma, PAC: Pancreatic adenocarcinoma

PD-1

Nivolumab

Nivolumab is a monoclonal antibody against PD-1. It got FDA approval as the first anti-PD-1 for the treatment of metastatic or unresectable melanoma in 2014 and small cell lung cancer (SCLC) in 2015 (60).

Currently, it has been approved to treat other cancers like non-small cell lung cancer (NSCLC), advanced RCC, hepatocellular carcinoma, and urothelial cancer (61-64).

Nivolumab has shown beneficial effects on patients with small-cell carcinoma of the pancreas. In a case report, a 59-year-old woman presented with hepatic and pancreatic tail lesions and a nodule in her right lung. Chemotherapy was started, and her computed tomography (CT) scan showed improvement after two cycles of chemotherapy. However, the lesions started to progress two months after the completion of the sixth cycle. Then, she received nivolumab, and the shrinkage of the hepatic and pancreatic lesions was seen in the CT scan after five weeks (65).

Like any other drug, nivolumab has some side effects like pneumonitis. For instance, in another case report, the pelvic and abdominal CT scan of a 53-year-old man showed pulmonary nodules, a pancreatic tail lesion, pleural effusion, and hepatic lesions. FOLFIRINOX was initiated for him. He consented to get into a clinical trial three weeks after the initiation of FOLFIRINOX. Therefore, gemcitabine, nab-paclitaxel, and nivolumab were used. Afterward, he presented with severe dyspnea, which was the result of pneumonitis (66).

Some studies are investigating the effects of nivolumab combined with other treatments to discover probable synergism between nivolumab and other drugs. In an ongoing phase Ib non-randomized single-arm interventional trial, metformin combined with nivolumab was used in 39 patients with pathological confirmed refractory or recurrent solid tumors such as pancreatic cancer and NSCLC. The researchers wanted to determine the best dose when nivolumab and metformin are administered together and to evaluate the safety and efficacy of this combination therapy. Currently, the results have shown acceptable efficacy, and scientists try to evaluate their safety in this clinical trial (67). These studies can open a new window for more investigation in the combination therapy field. There are a lot of ongoing trials that are utilizing nivolumab as an anti-PD-1 antibody (Table 2).

Table 2. Ongoing trials on Nivolumab

Trial number	Trial type	Phase	Status	Estimated N	Trial design	Treatment arms	Patient population	Drug	Results
NCT03599362	Interventional	II	Recruiting	20	N/A	A: Nivolumab, Cabiralizumab, SBRT	PC	Nivolumab, Cabiralizumab	N/A
NCT03697564	Interventional	II	Not yet recruiting	40	N/A	A: Gemcitabine, Nivoluma, Cabiralizumab	Stage IV PC	Gemcitabine, Nivolumab, Cabiralizumab	N/A
NCT03563248	Interventional	II	Recruiting	160	Randomized	A: FOLFIRINOX, SBRT, Surgery B: FOLFIRINOX, Losartan, SBRT, Surgery C: FOLFIRINOX, Losartan, SBRT, Nivolumab, Surgery D: FOLFIRINOX, SBRT, Nivolumab, Surgery	PC	FOLFIRINOX, Losartan, Nivolumab	N/A
NCT03161379	Interventional	II	Recruiting	50	N/A	A: CY, GVAX, Nivolumab, SBRT	PC	CY, GVAX vaccine, Nivolumab, SBRT	N/A
NCT03519308	Interventional	I	Recruiting	20	N/A	A: Nivolumab, Nab-paclitaxel, Gemcitabine, Paricalcitol B: Nivolumab, Nab-paclitaxel, Gemcitabine	PC	Nivolumab, Nab-paclitaxel, Gemcitabine, Paricalcitol	N/A
NCT03336216	Interventional	II	Recruiting	160	Randomized	A: Nab-paclitaxel, Onivyde, Fluorouracil, Gemcitabine, Leucovorin, Irinotecan Hydrochloride B: Nivolumab, Cabiralizumab C: Cabiralizumab, Nab-paclitaxel, Nivolumab, Gemcitabine D: Cabiralizumab, Nivolumab, Fluorouracil, Oxaliplatin, Leucovorin	Advanced PC	Cabiralizumab, Nab-paclitaxel, Onivyde, Nivolumab, Fluorouracil, Gemcitabine, Oxaliplatin, Leucovorin, Irinotecan Hydrochloride	N/A

Cont. table 2

NCT03190265	Interventional	II	Recruiting	63	Randomized	A: CY, Nivolumab, Ipilimumab, GVAX, CRS-207 B: Nivolumab, Ipilimumab, GVAX, CRS-207	PC	CY, Nivolumab, Ipilimumab, GVAX, CRS-207	N/A
NCT03785210	Interventional	II	Not yet recruiting	27	N/A	A: Nivolumab, Tadalafil, Vancomycin	Hepatocellular carcinoma Hepatocellular cancer Metastatic PC Metastatic CC Metastatic liver cancer	Nivolumab, Tadalafil, Vancomycin	N/A
NCT03184870	Interventional	I/ II	Recruiting	348	Non-randomized	A: BMS-813160, 5-FU, Leucovorin B: BMS-813160, Nab-paclitaxel, Gemcitabine C: BMS-813160, Nivolumab D: BMS-813160, Nab/paclitaxel, Gemcitabine, Nivolumab E: 5-FU, Leucovorin, Irinotecan F: Nab-paclitaxel, Gemcitabine G: BMS-813160	CC PC	BMS-813160, Nivolumab, Nab-paclitaxel, Gemcitabine, 5-FU, Leucovorin, Irinotecan	N/A
NCT03250273	Interventional	II	Recruiting	54	Non-randomized	A (Cholangiocarcinoma): Entinostat, nivolumab B (PC): Entinostat, nivolumab	Cholangiocarcinoma PC Metastatic PC Unresectable or Metastatic Cholangiocarcinoma	Entinostat, Nivolumab	N/A
NCT03404960	Interventional	I/ II	Recruiting	84	Randomized	A: Niraparib, Nivolumab B: Niraparib, Ipilimumab	PAC	Niraparib, Nivolumab, Ipilimumab	N/A
NCT03098550	Interventional	I/ II	Active, not recruiting	120	N/A	A (TNBC and PAC): Nivolumab, Daratumumab B (NSCLC): Nivolumab	Advanced cancer	Nivolumab, Daratumumab	N/A
NCT03767582	Interventional	I/ II	Not yet recruiting	30	Randomized	A (phase Ⅰ): SBRT, Nivolumab, GVAX, BMS-813160 B (phase Ⅱ): SBRT, Nivolumab, BMS-813160 C (phase Ⅱ): SBRT, Nivolumab, GVAX, BMS-813160	Locally advanced PDAC, PDAC	SBRT, Nivolumab, BMS-813160, GVAX	N/A
NCT03806309	Interventional	II	Not yet recruiting	156	Randomized	A: FOLFIRI B: OSE2101 C: Nivolumab	PDAC Locally advanced cancer Metastatic cancer	FOLFIRI, OSE2101, Nivolumab	N/A

SBRT: Stereotactic body radiotherapy, N: Number of participants, N/A: Not available, CY: Cyclophosphamide, 5-FU: 5-fluorouracil, TNBC: Triple-negative breast cancer, PAC: Pancreatic adenocarcinoma, NSCLC: Non-small cell lung cancer, PDAC: Pancreatic ductal adenocarcinoma, PC: Pancreatic cancer, CC: Colorectal cancer

A non-randomized single-arm phase Ⅰb/Ⅱ study has been started in 2015 on 33 patients with advanced cancers, including pancreatic cancer, RCC, SCLC, endometrial carcinoma, and colorectal cancer. This clinical trial had three arms in each arm nivolumab, and one or two of some other chemotherapeutic drugs, including temsirolimus, irinotecan, and capecitabine had been used. The purposes of this study were to determine the OS by measuring the time between terminated treatment to death, evaluating changes in blood proteins and tumor DNA, treatment-related AEs, and responses of the tumors (68). In a very similar non-randomized phase Ⅰa/Ⅰb study, scientists are evaluating the effects of cabiralizumab in combination with nivolumab on 295 patients with advanced solid tumors, pancreatic cancer, ovarian cancer, RCC, and malignant glioma. It has three experimental arms, nivolumab was used for two arms, and cabiralizumab was administrated for all three arms. The goals of this trial were the same as the previous study but antibodies against nivolumab and cabiralizumab, movement of cabiralizumab in the body, and the response of the body was also examined. In other words, the pharmacokinetic of cabiralizumab and pharmacodynamics biomarkers of CD8 and CD68, proteins that are highly expressed in T cells and macrophages, were assessed to detect the changes in the level of macrophages and T cells (69). In another single-arm phase Ⅱ study on 80 patients with pancreatic cancer and microsatellite stable/unstable colorectal cancer, a combination of an anti-CTLA-4 antibody (ipilimumab), an anti-PD-1 antibody (nivolumab), and radiation therapy was used to determine the disease control rate and OS (70).

Pembrolizumab

Pembrolizumab (MK-3475, Lambrolizumab), a humanized monoclonal immunoglobulin G4 (IgG4), is a PD-1 immune checkpoint inhibitor that could attach to PD-1 on the cell membrane of T lymphocytes and interrupt binding of PD-1 to its ligands, PDL-1, and PDL-2. As a result, tumor cells cannot suppress the immune system, and T cells can kill the tumor cells. Pembrolizumab has been approved for the treatment of gastric cancer, NSCLC, head and neck squamous cell carcinoma, and Hodgkin's lymphoma (71-74).

Weiss *et al*., have done a non-randomized phase I study to determine the recommended dose for a phase II study and also to assess the safety and efficacy of the combination of pembrolizumab and some other chemotherapeutic drugs like gemcitabine, docetaxel, nab-paclitaxel, and vinorelbine to evaluate the immune-related adverse events (irAEs), the rate of OS and PFS. Fifty patients enrolled in this trial. Eleven of them had PDAC and were categorized as arm 3. The rest of them had other types of cancer and were divided into five arms and followed for about seven months. The patients in arm 3 were also divided into two subgroups in one of them the patients had not received any treatment for PDAC (arm 3a) and in another, they had taken therapy before (arm 3b). Two mg/kg pembrolizumab was injected interavenously over 30 minutes every three weeks for each arm. Also, patients in arms 1, 2, 3, and 4 received gemcitabine. Docetaxel in arm 2, nab-paclitaxel in arm 3, vinorelbine in arm 4, irinotecan in arm 5, and liposomal doxorubicin in arm 6 were also administered. Two patients were replaced, and one patient did not take the treatment. All 47 patients who ended the first endpoint experienced treatment-emergent adverse events (TEAEs), events that did not exist before the new treatment, or got worse because of pretreatment conditions. Patients in arm 2 had the highest percent of grade 3-4 irAEs like hypoxia, dyspnea, syncope, and device infection. Grade 3-4 irAEs were decreased after initiating dexamethasone. The best partial tumor response was in patients in arms 5, 3, 6, and 4 with 33.3%, 22.2%, 14.3%, and 8.3% response, respectively. The mean OS rate among 11 PDAC patients was 9.12 months. Also, 66.7% of the patients in arm 3a showed a stable condition which was the highest percentage among other arms (75). This trial continued to phase Ⅱ to represent immune-related response criteria (irRECIST) as well as the abovementioned purposes. It showed that OS decreased gradually, and the OS for patients in arm 3a who had never taken treatment for their PDAC was 15 months. All of the patients in arm 3 who had received gemcitabine, nab-paclitaxel, and pembrolizumab drugs showed AEs and 70% of them were grade 3-4. Additionally, a negative correlation between PFS and irRECIST was found (76).

A randomized phase I/II clinical trial has been done on 22 resectable or borderline resectable pancreatic cancer patients to evaluate the safety and number of tumor-infiltrating lymphocytes, which are a kind of immune cells that attack the tumor cells and can be used for cancer therapy. This study had two arms. Pembrolizumab and neoadjuvant chemoradiation therapy was administered for 14 enrolled patients in arm A, and only neoadjuvant chemoradiation therapy was administered for 8 patients in arm B. The safety of using the combination of pembrolizumab and chemoradiation therapy was reported in this trial. However, some

treatment-related toxicities were observed in both arms, such as lymphopenias, diarrhea, and elevated level of alkaline phosphatase (77,78). Also, another study reported dermatological AEs such as grade 3 ulcerative oral mucositis in a patient with lung adenocarcinoma who had received pembrolizumab (79).

There are other phases I and II trials on pembrolizumab (Table 3).

Table 3. Some ongoing trials on Pembrolizumab

Trial number	Trial type	Phase	Status	Estimated N	Trial design	Treatment arms	Patient population	Drug	Results
NCT03168139	Interventional	I/II	Active, not recruiting	20	N/A	A: Olaptesed pego (monotherapy) B: Olaptesed pego and pembrolizumab	Metastatic CC Metastatic PC	Olaptesed pego, Pembrolizumab	N/A
NCT02826486	Interventional	II	Active, not recruiting	37 (A)	N/A	A: BL-8040 (monotherapy) B: BL-8040, Pembrolizumab (combination therapy)	Metastatic PC	BL-8040, Pembrolizumab	N/A
NCT03153410	Interventional	I	Recruiting	12	N/A	A: CY, GVAX, Pembrolizumab, IMC-CS4	PC	CY, GVAX, Pembrolizumab, IMC-CS4	N/A
NCT03432676	Interventional	II	Withdrawn	0 A	N/A	A: Pembrolizumab, Epacadostat	PAC	Pembrolizumab, Epacadostat	N/A
NCT03634332	Interventional	II	Not yet recruiting	35	N/A	A: Pembrolizumab, PEGPH20	PDAC PC Pancreatic neoplasms	Pembrolizumab, PEGPH20	N/A
NCT03006302	Interventional	II	Recruiting	70	Randomized	A: Epacadosta, Pembrolizumab, CY, GVAX, CRS-207 B: Epacadosta, Pembrolizumab, CRS-207	Metastatic PC	Epacadostat, Pembrolizumab, CRS-207, CY, GVAX	N/A
NCT02713529	Interventional	I/II	Active, not recruiting	116 A	N/A	A: AMG820, Pembrolizumab	CC PC NSCLC	AMG820, Pembrolizumab	N/A
NCT03716596	Interventional	I	Recruiting	36	Non-randomized	A: SBRT, Pembrolizumab	PC	SBRT, Pembrolizumb	N/A
NCT03095781	Interventional	I	Recruiting	50	N/A	A: XL888, Pembrolizumab	PC Gastrointestinal cancer	XL888, Pembrolizumab	N/A
NCT03043664	Interventional	I/II	Recruiting	26	N/A	A: Pembrolizumab, Somatuline depot	Gastroenteropancreatic neuroendocrine tumors	Pembrolizumab, Somatuline depot	N/A
NCT03727880	Interventional	II	Not yet recruiting	36	Randomized	A: Pembrolizumab, Defactinib B: Pembrolizumab	Resectable PDAC PDAC	Pembrolizumab, Defactinib	N/A

N/A: Not available, CY: Cyclophosphamide, SBRT: Stereotactic body radiotherapy, CC: Colorectal cancer, A: Acute, PC: Pancreatic cancer, PAC: Pancreatic adenocarcinoma, PDAC: Pancreatic ductal adenocarcinoma, NSCLC: Non-small cell lung cancer, ST: Solid tumors, N: Number of participants

NCT02648282 is an interventional phase II study with one arm in which GVAX, cyclophosphamide, stereotactic body radiotherapy, and 200 mg pembrolizumab were administered to patients with locally advanced pancreatic adenocarcinoma (48). NCT02907099 is another phase II trial that pembrolizumab and BL-8040, which is an antagonist of CXC chemokine receptor 4 (CXCR4), were administered to determine overall response rate (ORR) and duration of response (DOR) (80). A non-

randomized phase I trial is ongoing to assess the safety of a combination of 7 mcg/kg paricalcitol, a vitamin D analogous, and 200 mg pembrolizumab in patients with resectable pancreatic cancer. Enrolled patients were divided into two arms, which are in arm A, pembrolizumab, and paricalcitol, and in arm B, those mentioned drugs plus chemotherapy with 125 mg/sq.m nab-paclitaxel and 1000 mg/sq.m gemcitabine was administered. Also, surgery was done in all patients after the termination of paricalcitol treatment (81). To evaluate the effects of pembrolizumab in combination with paricalcitol by measuring the difference in disease progression after six months of the treatment initiation, a double-blind, randomized, placebo-controlled phase II study was done in 24 patients with advanced or metastatic pancreatic adenocarcinoma. Pembrolizumab and paricalcitol were administered in the active group, and pembrolizumab and placebo were used in the placebo group (82).

Expression of PDL-1, PD-1, and CTLA-4 are promoted by hypomethylating agents through demyelination of methylated CpG sites so that the combination of the hypomethylating agents with immune checkpoint inhibitors has synergistic effects (83). To assess the efficiency and safety of using pembrolizumab combined with azacitidine, which is a hypomethylating agent, a non-randomized phase II clinical trial is ongoing in patients with locally advanced or metastatic PDAC. This trial has only one arm, and all 31 enrolled patients will receive pembrolizumab and azacitidine. Serum factors and biopsy results will be analyzed to detect treatment progression (84).

PDL-1

Atezolizumab

Atezolizumab (Tecentriq, MPDL3280A) is an IgG1 monoclonal antibody against PDL-1 that inhibits the binding of PDL-1 to PD-1 and B7.1 (CD80) receptors. It was approved by the FDA for the treatment of urothelial carcinoma and platinum-resistant metastatic NSCLC in 2016 (85,86).

Ongoing trials that utilized atezolizumab in the treatment of pancreatic cancer are few. NCT03193190 is a multiple-drug, randomized, ongoing phase I/II clinical trial, and it aims to evaluate the efficacy and safety of multiple immune-based drug therapy in patients with PDAC. This trial includes two cohort studies. Enrolled patients in the first study had not taken any previous systemic therapy, but patients in the second cohort had. Each cohort group includes a control arm and a few experimental arms. The control arm in the first cohort took nab-paclitaxel and gemcitabine whereas, nab-paclitaxel plus gemcitabine or leucovorin calcium, fluorouracil, and oxaliplatin (FOLFOX-6) were used for the control arm in the second cohort. Atezolizumab, selicrelumab, bevacizumab, and emactuzumab were administered for the three experimental arms in the first cohort, and atezolizumab, cobimetinib, PEGPH20, BL-8040, RO6874281, and emactuzumab were used for the six experimental arms in the second cohort (87).

Avelumab

Avelumab (MSB0010718C), also called Bavencio, is an IgG1 human monoclonal antibody that binds to PDL-1 like atezolizumab. It can stimulate antibody-dependent cell-mediated cytotoxicity, which has antitumor activity (88). Thyroid disorders and rash are the most common avelumab-related AEs, respectively, but hepatitis, colitis, myositis, and pneumonitis may also occur (89).

Most avelumab clinical trials are ongoing (Table 4). NCT01772004 is a multi-center open-label phase I study on 1758 enrolled patients with solid tumors including NSCLC, RCC, mesothelioma, colorectal, urothelial, gastric, ovarian, prostate, head and neck, and breast cancers. Avelumab is administered to the patients of this cohort and this trial aimed to evaluate the dose-limiting toxicity of this drug (90). Also, 53 participants in this study were divided into four blocks to find the best dose of avelumab for solid tumors. One, 3, 10, and 20 mg/kg of avelumab were infused for participants in groups 1-4, respectively. The results showed that the best dose was 20 mg/kg, which opened a new way for further phase II/III trials (90). Additionally, several studies had been done following NCT01772004, which showed promising results in the safety and/or efficacy of avelumab in mesothelioma (91), adrenocortical cancer (92), urothelial cancer (93), and NSCLC (94).

NCT03481920 is a multi-center, open-label, non-randomized phase I clinical trial on 7 patients with chemotherapy-resistant advanced or locally advanced PDAC. Ten mg/kg avelumab and PEGylated recombinant human hyaluronidase PH20 (PEGPH20), a drug that decreases hyaluronic acid and has antitumor effects, were infused to the only arm of this study to assess the safety and pharmacodynamic effects of the combination (95). In another phase II trial, patients with pancreatic cancer were divided into two arms, and gemcitabine, nab-paclitaxel, and hydroxychloroquine were administered for both arms, but avelumab was just used for the first group. Therefore, researchers could

find the effects of gemcitabine, nab-paclitaxel, and hydroxychloroquine alone or in combination with avelumab on recovery or exacerbation of pancreatic tumors (96).

Table 4. Ongoing clinical trials on Avelumab

Trial number	Trial type	Phase	Status	Estimated N	Trial design	Treatment arms	Patient population	Drug	Results
NCT03451773	Interventional	I/II	Suspended	41	Non-randomized	A: M7824 de-escalation, Gemcitabine 1000 mg/m2 B: M7824 de-escalation, Gemcitabine 600 mg/m2 C: M7824 expansion, Gemcitabine 1000 mg/m2 D: M7824 expansion, Gemcitabine 600 mg/m2	PC PN	M7824, Gemcitabine	N/A
NCT03387098	Interventional	I/II	Active, not recruiting	173	N/A	A: NANT vaccine	PC	NANT pancreatic cancer vaccine (including avelumab)	N/A
NCT03329248	Interventional	I/II	Active, not recruiting	80	N/A	A: NANT vaccine	PC	NANT pancreatic cancer vaccine (including avelumab)	N/A
NCT03563144	Interventional	II	Not yet recruiting	1064	Randomized	A: NANT B: Gemcitabine, Nab-paclitaxel C: Gemcitabine	Metastatic PC	NANT, Gemcitabine, Nab-paclitaxel	N/A
NCT03637491	Interventional	II	Recruiting	127	Randomized	A: Avelumab, Binimetinib B: Avelumab, Binimetinib, Talazoparib	PC NSCLC	Avelumab, Binimetinib, Talazoparib	N/A

N/A: Not available, PC: Pancreatic cancer, PN: Pancreatic neoplasms, mg/m2: Milligram per square meters, NSCLC: Non-small cell lung cancer, N: number of participants

Combination therapy and vaccines

As was mentioned, most of the immune checkpoint inhibitors were approved for melanoma at first. It has been shown that a combination of different kinds of immune checkpoint inhibitors with each other or cancer vaccines usually leads to better outcomes (97,98). A phase 3 multi-centered, randomized, and double-blind study was conducted on 945 patients with stage III or IV melanoma who were divided into three groups. Ipilimumab for the first group, nivolumab for the second group, and a combination of ipilimumab and nivolumab were administered for the patients in the third group to evaluate the efficacy of combination therapy by measuring OS, PFS, and ORR. The results showed that the rate of complete response in the third group was higher than in the others. The median PFS for the combination therapy group was 11.5 months, while for the first and the second groups were 2.9 and 6.9 months, respectively (99).

Cancer vaccines are anti-cancer therapies against tumor cells by stimulating immune cells with tumor antigens (100). Most cancer vaccines aim to induce cytotoxic T lymphocytes (CTLs) by tumor-specific antigens like commonly expressed peptides derived from tumor cells (101). The advantages of cancer vaccines include a durable immune response because of memory cells, fewer adverse effects than other treatment modalities, and more specificity (102). Checkpoint molecules and immunosuppressive cytokines are some obstacles to cancer vaccines' functions and should be considered in enhancing their efficacy (103). These vaccines are becoming a new field to do clinical trials. For instance, the NANT cancer vaccine, a combination of metronomic low-dose radiation therapy and chemotherapy that is regulated by immunotherapy to activate the immune system, was administered to three

pancreatic cancer patients in a phase I/II trial. The primary goal was to evaluate AEs. Patients who had some conditions such as not having severe progressive disease entered phase Ⅱ, and continued this trial for one more year to assess the efficacy of this treatment (69).

A combination of vaccines and immune checkpoint inhibitors has also shown promising results in patients with pancreatic cancer. A phase Ib study was done at Johns Hopkins University in previously treated PDAC patients to assess the safety of 10 mg/kg ipilimumab alone or combined with a pancreatic cancer vaccine called GVAX, which includes pancreatic tumor cells and granulocyte-macrophage colony-stimulating factor. They randomly assigned the patients into two groups that were similar in baseline characteristics. In one of the groups, ipilimumab and GVAX were administered. In another group, only ipilimumab was administered. AEs such as hypophysitis, colitis, flu-like symptoms, and other rare effects were observed. These irAEs were identical to the findings of other studies that had tested ipilimumab at this dose. Median OS in patients who got ipilimumab alone was 2.1 months less than another group (3.6 vs. 5.7 months). It was also represented that one-year OS in patients who were administered ipilimumab and GVAX is 20% higher than in patients who were treated with only ipilimumab. Therefore, ipilimumab has beneficial effects as an immunotherapeutic drug in patients with pancreatic cancer and based on these results, it can have a better survival rate in combination with other therapies (97). Another phase IIb, randomized, controlled, and open-label trial was conducted on 303 patients with previously treated metastatic pancreatic adenocarcinoma. The study had three arms that cyclophosphamide/GVAX and CRS-207, a live-attenuated Listeria-based cancer vaccine, in arm A, CRS-207 in arm B, and single-agent chemotherapy based on physician's choice in arm C was administered. The median OS in these arms were 3.7, 5.4, and 4.6, respectively, and was concluded that the combination of CRS-207 and cyclophosphamide/GVAX does not improve survival significantly (104).

Although some viruses like human papillomavirus may lead to cancer, some of them are used for cancer therapy in combination with other drugs, including cancer vaccines or immune checkpoint inhibitors. For instance, NCT03723915 is a phase II clinical trial in those patients with PAC were treated with pembrolizumab and pelareorep (Reolysin), which contains reoviridae. Reoviridae are double-stranded RNA viruses that have shown effective clinical results in the treatment of patients with cancer (105). However, another study showed that participants who were treated with pelareorep in combination with paclitaxel and/or carboplatin did not have a significant response in phase II clinical trial. In this trial, the patients were divided into two arms. In arm A, paclitaxel, and carboplatin, and in arm B, pelareorep, paclitaxel and carboplatin were administered. The PFS and OS of arm B were higher than arm A, but they were not significant (*P*:0.6 and 0.68, respectively) (106).

Immune checkpoint inhibitors are a group of immunotherapeutic drugs, and even though it does not pass a long time since their approval, many clinical trials had been done that showed promising results in the safety and efficacy of these drugs, and many trials are still ongoing. Combination therapy of immune checkpoint inhibitors and other traditional and modern methods can increase the rate of successful treatments and decrease the AEs to the lowest possible level. Table 5 concretes the comparison between chemotherapeutics and immune checkpoint inhibitors toxicities. Also, more trials should be done to assess the safety and efficacy of the immune checkpoint inhibitors, especially in combination with cancer vaccines and viruses in different types of tumors mainly in cancers for that other therapeutic methods do not show a good response and have many morbidities.

Table 5. Adverse effects of chemotherapy versus immune checkpoint inhibitors (46,107)

Chemotherapy	Immune checkpoints inhibitors
Hepatotoxicity	Skin rash
Renal toxicity	Hypothyroidism
Neuropathy	Hypophysitis
Electrolytes imbalance	Pneumonitis
Infection	Hepatitis
Constitutional symptoms	Colitis
Gastrointestinal disorders	
Cardiovascular diseases	

Table S1. Search strategy for each database

Database	Query
PubMed and Web of science	#1. "Pancreatic Neoplasms"[Mesh] #2. Neoplasm, Pancreatic[Ti/Ab] OR "Pancreatic Neoplasm"[Ti/Ab] OR "Pancreas Neoplasms"[Ti/Ab] OR Neoplasm, Pancreas[Ti/Ab] OR Neoplasms, Pancreas[Ti/Ab] OR "Pancreas Neoplasm"[Ti/Ab] OR Neoplasms, Pancreatic[Ti/Ab] OR "Cancer of Pancreas"[Ti/Ab] OR "Pancreas Cancers"[Ti/Ab] OR "Pancreas Cancer"[Ti/Ab] OR Cancer, Pancreas[Ti/Ab] OR Cancers, Pancreas[Ti/Ab] OR "Pancreatic Cancer"[Ti/Ab] OR Cancer, Pancreatic[Ti/Ab] OR Cancers, Pancreatic[Ti/Ab] OR "Pancreatic Cancers"[Ti/Ab] OR "Cancer of the Pancreas"[Ti/Ab] OR "pancreatic neoplasms"[Ti/Ab] #3. "Therapeutics""[Mesh] #4. Therapeutic[Ti/Ab] OR Therapy[Ti/Ab] OR Therapies[Ti/Ab] OR Treatment[Ti/Ab] OR Treatments[Ti/Ab] OR Therapeutics[Ti/Ab] #5. "Ipilimumab""[Mesh] #6. "Anti-CTLA-4 MAb Ipilimumab""[Ti/Ab] OR ""Anti CTLA 4 MAb Ipilimumab""[Ti/Ab] OR Ipilimumab, Anti-CTLA-4 Mab[Ti/Ab] OR Yervoy[Ti/Ab] OR ""MDX 010""[Ti/Ab] OR MDX010[Ti/Ab] OR MDX-010[Ti/Ab] OR MDX-CTLA-4[Ti/Ab] OR ""MDX CTLA 4""[Ti/Ab] OR Ipilimumab[Ti/Ab])" #7. "Nivolumab""[Mesh] #8. Opdivo[Ti/Ab] OR ONO-4538[Ti/Ab] OR ""ONO 4538""[Ti/Ab] OR ONO4538[Ti/Ab] OR MDX-1106[Ti/Ab] OR ""MDX 1106""[Ti/Ab] OR MDX1106[Ti/Ab] OR BMS-936558[Ti/Ab] OR ""BMS 936558""[Ti/Ab] OR BMS936558[Ti/Ab] OR nivolumab[Ti/Ab] #9. "pembrolizumab"" [Supplementary Concept] #10. Lambrolizumab[Ti/Ab] OR Keytruda[Ti/Ab] OR MK-3475[Ti/Ab] OR pembrolizumab[Ti/Ab] #11. "atezolizumab" [Supplementary Concept] #12. anti-PDL1[Ti/Ab] OR immunoglobulin G1, anti-(human CD antigen CD274) (human monoclonal MDPL3280a heavy chain), disulfide with human monoclonal MDPL3280a kappa-chain, dimer[Ti/Ab] OR MPDL3280A[Ti/Ab] OR Tecentriq[Ti/Ab] OR RG7446[Ti/Ab] OR RG-7446[Ti/Ab] OR atezolizumab[Ti/Ab] #13. "avelumab" [Supplementary Concept] #14. MSB0010718C[Ti/Ab] OR avelumab[Ti/Ab], #15. #1 OR #2, #16. #3 OR #4, #17. #5 OR #6, #18. #7 OR #8, #19. #9 OR #10, #20. #11 OR #12, #21. #13 OR #14, #22. #15[AF] AND #16[AF] AND #17[AF], #23. #15[AF] AND #16[AF] AND #18[AF], #24. #15[AF] AND #16[AF] AND #19[AF], #25. #15[AF] AND #16[AF] AND #20[AF], #26. #15[AF] AND #16[AF] AND #21[AF]
Scopus	#1. Neoplasm, Pancreatic or "Pancreatic Neoplasm" or "Pancreas Neoplasms" or Neoplasm, Pancreas or Neoplasms, Pancreas or "Pancreas Neoplasm" or Neoplasms, Pancreatic or "Cancer of Pancreas" or "Pancreas Cancers" or "Pancreas Cancer" or Cancer, Pancreas or Cancers, Pancreas or "Pancreatic Cancer" or Cancer, Pancreatic or Cancers, Pancreatic or "Pancreatic Cancers" or "Cancer of the Pancreas" or "pancreatic neoplasms", #2. Therapeutic or Therapy or Therapies or Treatment or Treatments or Therapeutics, #3. "Anti-CTLA-4 MAb Ipilimumab" or "Anti CTLA 4 MAb Ipilimumab" or Ipilimumab, Anti-CTLA-4 Mab or Yervoy or "MDX 010" or MDX010 or MDX-010 or MDX-CTLA-4 or "MDX CTLA 4" or Ipilimumab, #4. Opdivo or ONO-4538 or "ONO 4538" or ONO4538 or MDX-1106 or "MDX 1106" or MDX1106 or BMS-936558 or "BMS 936558" or BMS936558 or nivolumab, #5. Lambrolizumab or Keytruda or MK-3475 or pembrolizumab, #6. anti-PDL1 or immunoglobulin G1, anti-(human CD antigen CD274) (human monoclonal MDPL3280a heavy chain), disulfide with human monoclonal MDPL3280a kappa-chain, dimer or MPDL3280A or Tecentriq or RG7446 or RG-7446 or atezolizumab, #7. MSB0010718C or avelumab
www.clinicaltrial.gov	Condition or disease: Pancreatic cancer Other terms: #1. Ipilimumab, #2. Nivolumab, #3. Pembrolizumab, #4. Atezolizumab, #5. Avelumab Status: All studies

References

1. Shetty AS, Menias CO. Rare Pancreatic Tumors. Magn Reson Imaging Clin N Am 2018;26:421-37.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin 2019;69:7-34.
3. Preziosi G, Oben JA, Fusai G. Obesity and pancreatic cancer. Surg Oncol 2014;23:61-71.
4. Alsamarrai A, Das SL, Windsor JA, Petrov MS. Factors that affect risk for pancreatic disease in the general population: a systematic review and meta-analysis of prospective cohort studies. Clin Gastroenterol Hepatol 2014;12:1635-44.e5; quiz e103.
5. Zhao Z, Yin Z, Pu Z, Zhao Q. Association Between Consumption of Red and Processed Meat and Pancreatic Cancer Risk: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol 2017;15:486-493.e10.
6. Wu QJ, Wu L, Zheng LQ, Xu X, Ji C, Gong TT. Consumption of fruit and vegetables reduces risk of pancreatic cancer: evidence from epidemiological studies. Eur J Cancer Prev 2016;25:196-205.
7. Haseeb A, Siddiqi MJS, Shaikh MF, Bowne WB. Laboratory Diagnosis of Gastrointestinal and Pancreatic Disorders. In: McPherson RA, Pincus MR. Henry's Clinical Diagnosis and Management by Laboratory Methods. 23 ed. New York: Elsevier Inc.; 2016:306-23.
8. Mukesh MGH, Harisinghani JWC, Weissleder R. Gastrointestinal Imaging. In: Mukesh MGH, Harisinghani JWC, Weissleder R, eds. Primer of Diagnostic Imaging. Amsterdam, Netherlands: Elsevier; 2018:124-216.
9. Ito T, Igarashi H, Jensen RT. Pancreatic neuroendocrine tumors: clinical features, diagnosis and medical treatment: advances. Best Pract Res Clin Gastroenterol 2012;26:737-53.
10. Nentwich MF, Bockhorn M, Konig A, Izbicki JR, Cataldegirmen G. Surgery for advanced and metastatic pancreatic cancer--current state and trends. Anticancer Res 2012;32:1999-2002.

11. Jilesen AP, van Eijck CH, Busch OR, van Gulik TM, Gouma DJ, van Dijkum EJ. Postoperative Outcomes of Enucleation and Standard Resections in Patients with a Pancreatic Neuroendocrine Tumor. World J Surg 2016;40:715-28.
12. Glimelius B, Hoffman K, Sjoden PO, Jacobsson G, Sellstrom H, Enander LK, et al. Chemotherapy improves survival and quality of life in advanced pancreatic and biliary cancer. Ann Oncol 1996;7:593-600.
13. Catenacci DV, Junttila MR, Karrison T, Bahary N, Horiba MN, Nattam SR, et al. Randomized Phase Ib/II Study of Gemcitabine Plus Placebo or Vismodegib, a Hedgehog Pathway Inhibitor, in Patients With Metastatic Pancreatic Cancer. J Clin Oncol 2015;33:4284-92.
14. Conroy T, Hammel P, Hebbar M, Ben Abdelghani M, Wei AC, Raoul JL, et al. FOLFIRINOX or Gemcitabine as Adjuvant Therapy for Pancreatic Cancer. N Engl J Med 2018;379:2395-406.
15. Attard CL, Brown S, Alloul K, Moore MJ. Cost-effectiveness of FOLFIRINOX for first-line treatment of metastatic pancreatic cancer. Curr Oncol 2014;21:e41-51.
16. Conroy T, Desseigne F, Ychou M, Ducreux M, Bouche O, Guimbaud R, et al. Randomized phase III trial comparing FOLFIRINOX (F: 5FU/leucovorin [LV], irinotecan [I], and oxaliplatin [O]) versus gemcitabine (G) as first-line treatment for metastatic pancreatic adenocarcinoma (MPA): Preplanned interim analysis results of the PRODIGE 4/ACCORD 11 trial. J Clin Oncol 2010;28:4010.
17. Moore MJ, Goldstein D, Hamm J, Figer A, Hecht JR, Gallinger S, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 2007;25:1960-6.
18. Rubinson DA, Wolpin BM. Therapeutic Approaches for Metastatic Pancreatic Adenocarcinoma. Hematol Oncol Clin North Am 2015;29:761-76.
19. Rombouts SJ, Mungroop TH, Heilmann MN, van Laarhoven HW, Busch OR, Molenaar IQ, et al. FOLFIRINOX in Locally Advanced and Metastatic Pancreatic Cancer: A Single Centre Cohort Study. J Cancer 2016;7:1861-6.
20. Sherman WH, Chu K, Chabot J, Allendorf J, Schrope BA, Hecht E, et al. Neoadjuvant gemcitabine, docetaxel, and capecitabine followed by gemcitabine and capecitabine/radiation therapy and surgery in locally advanced, unresectable pancreatic adenocarcinoma. Cancer 2015;121:673-80.
21. Khorana AA, Mangu PB, Berlin J, Engebretson A, Hong TS, Maitra A, et al. Potentially Curable Pancreatic Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol 2017;35:2324-8.
22. Boothe D, Clyde JW, Christensen M, Patel SB, Lloyd S. A comprehensive analysis of clinical trials including both immunotherapy and radiation therapy. J Radiat Oncol 2018;7:223-32.
23. Goodman KA, Hajj C. Role of radiation therapy in the management of pancreatic cancer. J Surg Oncol 2013;107:86-96.
24. Reese AS, Lu W, Regine WF. Utilization of intensity-modulated radiation therapy and image-guided radiation therapy in pancreatic cancer: is it beneficial? Semin Radiat Oncol 2014;24:132-9.
25. Jung J, Yoon SM, Park JH, Seo DW, Lee SS, Kim MH, et al. Stereotactic body radiation therapy for locally advanced pancreatic cancer. PloS one 2019;14:e0214970.
26. Jethwa KR, Tryggestad EJ, Whitaker TJ, Giffey BT, Kazemba BD, Neben-Wittich MA, et al. Initial experience with intensity modulated proton therapy for intact, clinically localized pancreas cancer: Clinical implementation, dosimetric analysis, acute treatment-related adverse events, and patient-reported outcomes. Adv Radiat Oncol 2018;3:314-21.
27. Ceha HM, van Tienhoven G, Gouma DJ, Veenhof CH, Schneider CJ, Rauws EA, et al. Feasibility and efficacy of high dose conformal radiotherapy for patients with locally advanced pancreatic carcinoma. Cancer 2000;89:2222-9.
28. Ben-Josef E, Schipper M, Francis IR, Hadley S, Ten-Haken R, Lawrence T, et al. A Phase I/II Trial of Intensity Modulated Radiation (IMRT) Dose Escalation With Concurrent Fixed-dose Rate Gemcitabine (FDR-G) in Patients With Unresectable Pancreatic Cancer. Int J Radiat Oncol Biol Phys 2012;84:1166-71.
29. Sideras K, Braat H, Kwekkeboom J, van Eijck CH, Peppelenbosch MP, Sleijfer S, et al. Role of the immune system in pancreatic cancer progression and immune modulating treatment strategies. Cancer Treat Rev 2014;40:513-22.
30. Weber J, Mandala M, Del Vecchio M, Gogas HJ, Arance AM, Cowey CL, et al. Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma. N Engl J Med 2017;377:1824-35.
31. Bang YJ, Kang YK, Catenacci DV, Muro K, Fuchs CS, Geva R, et al. Pembrolizumab alone or in combination with chemotherapy as first-line therapy for patients with advanced gastric or gastroesophageal junction adenocarcinoma: results from the phase II nonrandomized KEYNOTE-059 study. Gastric Cancer 2019;22:828-37.
32. Balar AV, Galsky MD, Rosenberg JE, Powles T, Petrylak DP, Bellmunt J, et al. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and

metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. Lancet 2017;389:67-76.
33. Kaufman HL, Russell J, Hamid O, Bhatia S, Terheyden P, D'Angelo SP, et al. Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial. Lancet Oncol 2016;17:1374-85.
34. Tawbi HA, Forsyth PA, Algazi A, Hamid O, Hodi FS, Moschos SJ, et al. Combined Nivolumab and Ipilimumab in Melanoma Metastatic to the Brain. N Engl J Med 2018;379:722-30.
35. Varga A, Piha-Paul S, Ott PA, Mehnert JM, Berton-Rigaud D, Morosky A, et al. Pembrolizumab in patients with programmed death ligand 1-positive advanced ovarian cancer: Analysis of KEYNOTE-028. Gynecol Oncol 2019;152:243-50.
36. Barlesi F, Vansteenkiste J, Spigel D, Ishii H, Garassino M, de Marinis F, et al. Avelumab versus docetaxel in patients with platinum-treated advanced non-small-cell lung cancer (JAVELIN Lung 200): an open-label, randomised, phase 3 study. Lancet Oncol 2018;19:1468-79.
37. Laplagne C, Domagala M, Le Naour A, Quemerais C, Hamel D, Fournie JJ, et al. Latest Advances in Targeting the Tumor Microenvironment for Tumor Suppression. Int J Mol Sci 2019;20:4719.
38. Hiraoka N, Onozato K, Kosuge T, Hirohashi S. Prevalence of FOXP3+ regulatory T cells increases during the progression of pancreatic ductal adenocarcinoma and its premalignant lesions. Clin Cancer Res 2006;12:5423-34.
39. Gabitass RF, Annels NE, Stocken DD, Pandha HA, Middleton GW. Elevated myeloid-derived suppressor cells in pancreatic, esophageal and gastric cancer are an independent prognostic factor and are associated with significant elevation of the Th2 cytokine interleukin-13. Cancer Immunol Immunother 2011;60:1419-30.
40. Esposito I, Menicagli M, Funel N, Bergmann F, Boggi U, Mosca F, et al. Inflammatory cells contribute to the generation of an angiogenic phenotype in pancreatic ductal adenocarcinoma. J Clin Pathol 2004;57:630-6.
41. Aparicio-Pages MN, Verspaget HW, Pena AS, Lamers CB. Natural killer cell activity in patients with adenocarcinoma in the upper gastrointestinal tract. J Clin Lab Immunol 1991;35:27-32.
42. Banerjee K, Kumar S, Ross KA, Gautam S, Poelaert B, Nasser MW, et al. Emerging trends in the immunotherapy of pancreatic cancer. Cancer Lett 2018;417:35-46.
43. Dubbs SB. The Latest Cancer Agents and Their Complications. Emerg Med Clin North Am 2018;36:485-92.
44. Narvaez J, Juarez-Lopez P, LLuch J, Narvaez JA, Palmero R, Garcia Del Muro X, et al. Rheumatic immune-related adverse events in patients on anti-PD-1 inhibitors: Fasciitis with myositis syndrome as a new complication of immunotherapy. Autoimmun Rev 2018;17:1040-5.
45. Sharpe AH, Pauken KE. The diverse functions of the PD1 inhibitory pathway. Nat Rev Immunol 2017;18:153-67.
46. Marin-Acevedo JA, Chirila RM, Dronca RS. Immune Checkpoint Inhibitor Toxicities. Mayo Clin Proc 2019;94:1321-9.
47. Fujii T, Naing A, Rolfo C, Hajjar J. Biomarkers of response to immune checkpoint blockade in cancer treatment. Crit Rev Oncol Hematol 2018;130:108-20.
48. Geng L, Huang D, Liu J, Qian Y, Deng J, Li D, et al. B7-H1 up-regulated expression in human pancreatic carcinoma tissue associates with tumor progression. J Cancer Res Clin Oncol 2008;134:1021-7.
49. Taube JM, Klein A, Brahmer JR, Xu H, Pan X, Kim JH, et al. Association of PD-1, PD-1 ligands, and other features of the tumor immune microenvironment with response to anti-PD-1 therapy. Clin Cancer Res 2014;20:5064-74.
50. Kelderman S, Heemskerk B, Van Tinteren H, Van Den Brom RRH, Hospers GAP, Van Den Eertwegh AJM, et al. Lactate dehydrogenase as a selection criterion for ipilimumab treatment in metastatic melanoma. Cancer Immunol Immunother 2014;63:449-58.
51. Langer CJ, Gadgeel SM, Borghaei H, Papadimitrakopoulou VA, Patnaik A, Powell SF, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. Lancet Oncol 2016;17:1497-508.
52. Overman MJ, McDermott R, Leach JL, Lonardi S, Lenz H-J, Morse MA, et al. Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study. Lancet Oncol 2017;18:1182-91.
53. Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, et al. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. N Engl J Med 2015;372:2509-20.
54. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010;363:711-23.
55. Johnson DB, Chandra S, Sosman JA. Immune Checkpoint Inhibitor Toxicity in 2018. JAMA 2018;320:1702-3.
56. Liu Y, Zheng P. How Does an Anti-CTLA-4 Antibody Promote Cancer Immunity? Trends Immunol 2018;39:953-6.
57. Binder KR. Niraparib + Ipilimumab or Nivolumab in

Progression Free Pancreatic Adenocarcinoma After Platinum-Based Chemotherapy (Parpvax). (Accessed April 11, 2023, at https://clinicaltrials.gov/ct2/show/NCT03404960.)
58. Chen I. Immune Checkpoint Inhibition in Combination With Radiation Therapy in Pancreatic Cancer or Biliary Tract Cancer Patients. (Accessed September 5, 2020, at https://clinicaltrials.gov/ct2/show/NCT02866383.)
59. Patel S. Nivolumab and Ipilimumab in Treating Patients With Rare Tumors (Accessed March 30, 2023, at https://clinicaltrials.gov/ct2/show/NCT02834013.)
60. La-Beck NM, Jean GW, Huynh C, Alzghari SK, Lowe DB. Immune Checkpoint Inhibitors: New Insights and Current Place in Cancer Therapy. Pharmacotherapy 2015;35:963-76.
61. Motzer RJ, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S, et al. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med 2015;373:1803-13.
62. El-Khoueiry AB, Sangro B, Yau T, Crocenzi TS, Kudo M, Hsu C, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. Lancet 2017;389:2492-502.
63. Brahmer J, Reckamp KL, Baas P, Crino L, Eberhardt WE, Poddubskaya E, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. N Engl J Med 2015;373:123-35.
64. Sharma P, Retz M, Siefker-Radtke A, Baron A, Necchi A, Bedke J, et al. Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial. Lancet Oncol 2017;18:312-22.
65. Ugwu JK, Nwanyanwu C, Shelke AR. Dramatic Response of a Metastatic Primary Small-Cell Carcinoma of the Pancreas to a Trial of Immunotherapy with Nivolumab: A Case Report. Case Rep Oncol 2017;10:720-5.
66. Costa RB, Al B, Yaghmai V, Costa RLB, Zhou HJ, Behdad A, et al. An Extremely Rapid Case of Pneumonitis with the Use of Nivolumab for Pancreatic Adenocarcinoma. Case Rep Oncol Med 2018;2018:6314392.
67. Kubo T, Ninomiya T, Hotta K, Kozuki T, Toyooka S, Okada H, et al. Study Protocol: Phase-Ib Trial of Nivolumab Combined With Metformin for Refractory/Recurrent Solid Tumors. Clin Lung Cancer. 2018;19:e861-4.
68. Lynch C. Study of Nivolumab Plus Chemotherapy in Patients With Advanced Cancer (NivoPlus). (Accessed July 2, 2018, at https://clinicaltrials.gov/ct2/show/study/NCT02423954.)
69. Lead M. Study of Cabiralizumab in Combination With Nivolumab in Patients With Selected Advanced Cancers (Accessed March 9, 2022, https://clinicaltrials.gov/ct2/show/study/NCT02526017.)
70. Hong T. Nivolumab and Ipilimumab and Radiation Therapy in MSS and MSI High Colorectal and Pancreatic Cancer (Accessed September 8, 2022, https://clinicaltrials.gov/ct2/show/NCT03104439).
71. Chen R, Zinzani PL, Fanale MA, Armand P, Johnson NA, Brice P, et al. Phase II Study of the Efficacy and Safety of Pembrolizumab for Relapsed/Refractory Classic Hodgkin Lymphoma. J Clin Oncol 2017;35:2125-32.
72. Herbst RS, Baas P, Kim DW, Felip E, Pérez-Gracia JL, Han JY, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet 2016;387:1540-50.
73. Seiwert TY, Burtness B, Mehra R, Weiss J, Berger R, Eder JP, et al. Safety and clinical activity of pembrolizumab for treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-012): an open-label, multicentre, phase 1b trial. Lancet Oncol 2016;17:956-65.
74. Fuchs CS, Doi T, Jang RWJ, Muro K, Satoh T, Machado M, et al. KEYNOTE-059 cohort 1: Efficacy and safety of pembrolizumab (pembro) monotherapy in patients with previously treated advanced gastric cancer. J Clin Oncol 2017;35:4003.
75. Weiss GJ, Waypa J, Blaydorn L, Coats J, McGahey K, Sangal A, et al. A phase Ib study of pembrolizumab plus chemotherapy in patients with advanced cancer (PembroPlus). Br J Cancer 2017;117:33-40.
76. Weiss GJ, Blaydorn L, Beck J, Bornemann-Kolatzki K, Urnovitz H, Schutz E, et al. Phase Ib/II study of gemcitabine, nab-paclitaxel, and pembrolizumab in metastatic pancreatic adenocarcinoma. Invest New Drugs 2018;36:96-102.
77. Katz MHG, Varadhachary GR, Bauer TW, Acquavella N, Merchant NB, Le TM, et al. Preliminary safety data from a randomized multicenter phase Ib/II study of neoadjuvant chemoradiation therapy (CRT) alone or in combination with pembrolizumab in patients with resectable or borderline resectable pancreatic cancer. J Clin Oncol 2017;35:4125.
78. Slingluff CL. Safety and Immunological Effect of Pembrolizumab in Resectable or Borderline Resectable Pancreatic Cancer (UVA-PC-PD101). (Accessed August 13, 2021, at https://clinicaltrials.gov/ct2/show/study/NCT02305186.)
79. Lederhandler MH, Ho A, Brinster N, Ho RS, Liebman TN, Lo Sicco K. Severe Oral Mucositis: A Rare Adverse Event of Pembrolizumab. J Drugs Dermatol 2018;17:807-9.

80. Fogelman D. Pembrolizumab and BL-8040 in Metastatic Pancreatic Cancer (Accessed March 9, 2023, at https://clinicaltrials.gov/ct2/show/study/NCT02907099.)
81. Goldstein J, Katz M. Preoperative Pilot Study to Assess Safety and Immunological Effect of Pembrolizumab (Keytruda®) in Combination With Paricalcitol With or Without Chemotherapy in Patients With Resectable Pancreatic Cancer. (Accessed February 9, 2023, https://clinicaltrials.gov/ct2/show/NCT02930902.)
82. Borazanci E, Jameson G, Chung V, Alistar A, Hoff DDV. A SU2C Catalyst® Trial of a PD1 Inhibitor With or Without a Vitamin D Analog for the Maintenance of Pancreatic Cancer. (Accessed December 27, 2022, at https://clinicaltrials.gov/ct2/show/NCT03331562).
83. Orskov AD, Treppendahl MB, Skovbo A, Holm MS, Friis LS, Hokland M, et al. Hypomethylation and up-regulation of PD-1 in T cells by azacytidine in MDS/AML patients: A rationale for combined targeting of PD-1 and DNA methylation. Oncotarget 2015;6:9612-26.
84. Safyan RA, Gonda T, Tycko B, Chabot JA, Manji GA, Schwartz GK. Phase II open-label, single-center study evaluating safety and efficacy of pembrolizumab following induction with the hypomethylating agent azacitidine in patients with advanced pancreatic cancer after failure of first-line therapy. J Clin Oncol 2018;36:1.
85. Rosenberg JE, Hoffman-Censits J, Powles T, van der Heijden MS, Balar AV, Necchi A, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet 2016;387:1909-20.
86. Krishnamurthy A, Jimeno A. Atezolizumab: A novel PD-L1 inhibitor in cancer therapy with a focus in bladder and non-small cell lung cancers. Drugs Today (Barc) 2017;53:217-37.
87. Roche HL. A Study of Multiple Immunotherapy-Based Treatment Combinations in Participants With Metastatic Pancreatic Ductal Adenocarcinoma (Morpheus-Pancreatic Cancer). (Accessed April 10, 2023, at https://clinicaltrials.gov/ct2/show/record/NCT03193190).
88. Julia EP, Amante A, Pampena MB, Mordoh J, Levy EM. Avelumab, an IgG1 anti-PD-L1 Immune Checkpoint Inhibitor, Triggers NK Cell-Mediated Cytotoxicity and Cytokine Production Against Triple Negative Breast Cancer Cells. Front Immunol 2018;9:2140.
89. Kelly K, Infante JR, Taylor MH, Patel MR, Wong DJ, Iannotti N, et al. Safety profile of avelumab in patients with advanced solid tumors: A pooled analysis of data from the phase 1 JAVELIN solid tumor and phase 2 JAVELIN Merkel 200 clinical trials. Cancer 2018;124:2010-7.
90. Heery CR, O'Sullivan-Coyne G, Madan RA, Cordes L, Rajan A, Rauckhorst M, et al. Avelumab for metastatic or locally advanced previously treated solid tumours (JAVELIN Solid Tumor): a phase 1a, multicohort, dose-escalation trial. Lancet Oncol 2017;18:587-98.
91. Hassan R, Thomas A, Nemunaitis JJ, Patel MR, Bennouna J, Chen FL, et al. Efficacy and Safety of Avelumab Treatment in Patients With Advanced Unresectable Mesothelioma: Phase 1b Results From the JAVELIN Solid Tumor Trial. JAMA Oncol 2019;5:351-7.
92. Le Tourneau C, Hoimes C, Zarwan C, Wong DJ, Bauer S, Claus R, et al. Avelumab in patients with previously treated metastatic adrenocortical carcinoma: phase 1b results from the JAVELIN solid tumor trial. J Immunother Cancer 2018;6:111.
93. Patel MR, Ellerton J, Infante JR, Agrawal M, Gordon M, Aljumaily R, et al. Avelumab in metastatic urothelial carcinoma after platinum failure (JAVELIN Solid Tumor): pooled results from two expansion cohorts of an open-label, phase 1 trial. Lancet Oncol 2018;19:51-64.
94. Gulley JL, Rajan A, Spigel DR, Iannotti N, Chandler J, Wong DJL, et al. Avelumab for patients with previously treated metastatic or recurrent non-small-cell lung cancer (JAVELIN Solid Tumor): dose-expansion cohort of a multicentre, open-label, phase 1b trial. Lancet Oncol 2017;18:599-610.
95. Rodriguez LM, Batle JF, Ponce CG. A Trial of PEGPH20 in Combination With Avelumab in Chemotherapy Resistant Pancreatic Cancer. (Accessed August 22, 2019, at https://clinicaltrials.gov/ct2/show/study/NCT03481920.)
96. Bahary N. Pre-Operative Trial (PGHA vs. PGH) for Resectable Pancreatic Cancer (17-134). (Accessed May 14, 2020, https://clinicaltrials.gov/ct2/show/study/NCT03344172.)
97. Le DT, Lutz E, Uram JN, Sugar EA, Onners B, Solt S, et al. Evaluation of ipilimumab in combination with allogeneic pancreatic tumor cells transfected with a GM-CSF gene in previously treated pancreatic cancer. J Immunother 2013;36:382-9.
98. Morse MA, Lyerly HK. Checkpoint blockade in combination with cancer vaccines. Vaccine 2015;33:7377-85.
99. Hodi FS, Chiarion-Sileni V, Gonzalez R, Grob JJ, Rutkowski P, Cowey CL, et al. Nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone in advanced melanoma (CheckMate 067): 4-year outcomes of a multicentre, randomised, phase 3 trial. Lancet Oncol 2018;19:1480-92.
100. Gray JE, Chiappori A, Williams CC, Tanvetyanon T, Haura EB, Creelan BC, et al. A phase I/randomized phase II study of GM.CD40L vaccine in combination with

CCL21 in patients with advanced lung adenocarcinoma. Cancer Immunol Immunother 2018;67:1853-62.

101. Sundar R, Rha SY, Yamaue H, Katsuda M, Kono K, Kim HS, et al. A phase I/Ib study of OTSGC-A24 combined peptide vaccine in advanced gastric cancer. BMC Cancer 2018;18:332.
102. Emens LA. Cancer vaccines: on the threshold of success. Expert opinion on emerging drugs. Expert Opin Emerg Drugs 2008;13:295-308.
103. Maeng H, Terabe M, Berzofsky JA. Cancer vaccines: translation from mice to human clinical trials. Curr Opin Immunol 2018;51:111-22.
104. Le DT, Picozzi VJ, Ko AH, Wainberg ZA, Kindler H, Wang-Gillam A, et al. Results from a Phase IIb, Randomized, Multicenter Study of GVAX Pancreas and CRS-207 Compared with Chemotherapy in Adults with Previously Treated Metastatic Pancreatic Adenocarcinoma (ECLIPSE Study). Clin Cancer Res 2019;25:5493-502.
105. Mahalingam D. Pembrolizumab and Pelareorep in Treating Patients With Advanced Pancreatic Cancer. (Accessed October 5, 2022, https://clinicaltrials.gov/ct2/show/record/NCT03723915.)
106. Noonan AM, Farren MR, Geyer SM, Huang Y, Tahiri S, Ahn D, et al. Randomized Phase 2 Trial of the Oncolytic Virus Pelareorep (Reolysin) in Upfront Treatment of Metastatic Pancreatic Adenocarcinoma. Mol Ther 2016;24:1150-8.
107. Chen J, Chen L, Yu J, Xu Y, Wang X, Zeng Z, et al. Metaanalysis of current chemotherapy regimens in advanced pancreatic cancer to prolong survival and reduce treatmentassociated toxicities. Mol Med Rep 2019;19:477-89.